REMARKS

Applicants acknowledge receipt of the Office Action mailed on November 28, 2003. Claims 1-25 are pending. Claims 1, 2, 5, 16, 17 and 20 have been amended to delete the term "purified" and to clarify that the chromium-containing compound excludes chromium yeasts. Support for the amendments can be found throughout the specification and in the original claims as filed. For example, support for the amendments can be found in paragraph **[0042]** of the specification. Claims 16-20 were rejected under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. Claims 1-25 were rejected under 35 U.S.C. §103 as unpatentable over de la Harpe et al. and Ostlund et al. Reconsideration and withdrawal of the present rejections in view of the amendments, comments, declaration, and Exhibit presented herein are respectfully requested.

Claims 16-20, as amended, comply with the written description requirement

Claims 16-20 were rejected under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. According to the Examiner, the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. Specifically, the phrase "purified chromium-containing compound" was objected to as lacking sufficient written description in the specification to satisfy 35 U.S.C. §112, first paragraph.

Claims 16, 17, and 20 have been amended to delete the term "purified", thereby obviating the rejection.

Regarding the term "consisting essentially of"

The Examiner indicated that the previous rejection under 35 U.S.C. §112, second paragraph has been removed. The Examiner accepted the arguments presented regarding the definition of the phrase "consisting essentially of" and opined that the claims "clearly state a 'basic and novel characteristic'" of the invention is the treatment of PCOS. Applicants wish to clarify that the "basic and novel characteristic" of the invention is not merely the treatment of PCOS as suggested by the Examiner. Rather, Applicants consider the basic and novel characteristic of the claimed invention to be the use of chromium in ameliorating symptoms associated with PCOS. As detailed in Applicants' response to the Final Office Action, the specification is clear regarding the purposes of including additional substances such as chelating

agents. Chelating agents play a supporting role in the invention by creating coordinated forms of chromium that are directly available for absorption without competition from other metals. As the specification clearly sets forth, the chelating agents serve to enhance the absorption of chromium. By enhancing the absorption of chromium into the body, more chromium become bioavailable, thus, less chromium is required to practice the invention. However, with or without the chelating agent, chromium leads to the reduction of PCOS symptoms. While these ingredients may be beneficial, they are not essential to the basic and novel characteristic of the invention, namely chromium for the amelioration of symptoms of PCOS.

Claims 1-25 are not obvious in view of de la Harpe et al. (U.S. Patent No. 5,980,905) and Ostlund et al. (U.S. Patent No. 5,550,166)

Claims 1-20 remain rejected and Claims 21-25 were newly rejected under 35 U.S.C. §103(a) as being unpatentable over de la Harpe et al. (U.S. Patent No. 5,980,905) ('905) in view of Ostlund et al. (U.S. Patent No. 5,550,166) ('166). As will be described in greater detail below, de la Harpe et al. teaches the administration of chromium picolinate for lowering serum glucose, supplementing dietary chromium, lowering serum lipid levels, and increasing lean body mass. Ostlund et al., in contrast, teaches the administration of pinitol, a carbohydrate, for treating symptoms of insulin resistance, including those symptoms in PCOS. According to the Examiner, de la Harpe et al. implicitly describes that chromium functions to decrease insulin resistance. Thus, the Examiner opines that the references, when combined, anticipate the claimed invention. Applicants disagree, as more fully set forth below.

A *prima facie* case of obviousness is established when three basic criteria are met. First, there must be some suggestion or motivation to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. §2143. Applicants maintain their position that the Examiner has failed to establish a *prima facie* case of obviousness. Moreover, Applicants assert that the cited references are not sufficient to support a *prima facie* case of obviousness. These matters are discussed in detail in the following sections.

There is no suggestion or motivation to combine de la Harpe et al. and Ostlund et al. to arrive at the claimed invention

De la Harpe et al. disclose and claim formulations of chromium with other ingredients and methods for reducing serum blood glucose, reducing hyperglycemia, stabilizing blood glucose levels, increasing lean body mass, reducing body fat, and reducing high levels of blood serum lipids by administering a chromium supplement. The '905 patent further discloses that dietary chromium supplementation has been observed to lead to numerous physiological changes and that chromium functions as a co-factor for insulin. According to the Examiner, de la Harpe also implicitly describes the role of chromium in decreasing insulin resistance. The Ostlund reference teaches a composition and method for the treatment of insulin resistance and related complications including PCOS that contains or utilizes an effective amount of pinitol, a derivative of pinitol, or a metabolite of pinitol. As discussed in previous responses to Office Actions, the '166 patent also describes the addition of elective ingredients that may be incorporated into the composition or used in the treatment method in addition to pinitol, including chromium yeast for an enteral formulation. See column 4, lines 44-61 of the Ostlund patent. According to the Examiner, it would have been obvious to combine the teachings of de la Harpe with the teachings of Ostlund to arrive at the claimed invention. Applicant disagrees.

The mere fact that the teachings of de la Harpe et al. and Ostlund et al. might be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. See *In re Mills*, 16 U.S.P.Q.2d 1430 (Fed Cir. 1990); See, also M.P.E.P. §2143.01. Both references are completely silent with respect to the benefits of administering a chromium complex for ameliorating the symptoms associated with PCOS because neither reference appreciated that chromium (rather than pinitol as suggested in the '166 patent) affected symptoms of PCOS such as insulin resistance.

According to the Examiner, the '905 patent discloses that chromium depletion leads to disturbed glucose metabolism and chromium acts as a cofactor for insulin. The Examiner further notes:

> It is well known that insulin stimulates fat and muscle cells to take up glucose. Since chromium complexes show an improvement in glucose tolerance, the ability of the body to transport glucose, as evidence by de la Harpe et al., and do not increase insulin production as some diabetes-type 2 drugs, the insulin must have been potentiated, as clearly disclosed by de la Harpe et al.

Thus, the Examiner reasons, insulin resistance must have been corrected to some degree in order to result in the positive outcome which is shown as improved glucose tolerance in diabetes-type 2 in order for glucose metabolism to be corrected. The Federal Circuit has made clear that '[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." See *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988). Applicants submit that this is precisely what the Examiner is attempting to accomplish.

Contrary to the position taken by the Examiner, neither the '905 reference nor the '166 reference teach or suggest a relationship between chromium supplementation and the alleviation of insulin resistance. As stated earlier, while the invention of de la Harpe teaches methods of treating conditions which can be symptoms of insulin resistance, e.g. hyperlipidemia, dyslipidemia and abnormal glucose tolerance, Applicants maintain that there is no indication in the de la Harpe reference that the compositions and methods taught therein would be effective in the treatment of insulin resistance itself. Hyperlipidemia, dyslipidemia and abnormal glucose tolerance are not definitive signs of insulin resistance and, as the Examiner agreed, can manifest in patients who are not afflicted with insulin resistance. Although the compositions and methods of de la Harpe could possibly be useful for treating hyperlipidemia and dyslipidemia that arise due to insulin resistance, there is no suggestion in de la Harpe that the compositions or methods disclosed therein would be effective at reducing insulin resistance itself, the underlying causes of insulin resistance or in treating other conditions which are closely associated with insulin resistance such as PCOS. Notably, the '905 reference is entirely silent with respect to the role of chromium in the treatment of PCOS. Given the lack of a definitive connection between the methods and compositions of de la Harpe and the purposes for the invention of Ostlund, there is no motivation absent impermissible hindsight to combine the teachings of the two references.

There is no reasonable expectation of success in modifying the reference teachings

Furthermore, a *prima facie* case for obviousness is established only when the Examiner provides references that would lead one of ordinary skill in the art to believe that he or she would have a reasonable expectation of success in practicing the claimed invention in view of the cited art. See *In re Merck & Co., Inc.*, 231 U.S.P.Q. 375 (Fed. Cir. 1986); M.P.E.P. §2143.02. Applicants respectfully submit that it is not reasonable to expect that an essential metal such as chromium as described in the de la Harpe et al. reference could be substituted for a carbohydrate such as pinitol as described in the Ostlund et al. reference to treat PCOS as is currently claimed.

Applicants note that the '166 patent provides no clinical data whatsoever regarding the effect of pinitol on the treatment of PCOS. Instead, PCOS is part of a laundry list of diseases in which insulin sensitivity is compromised. This lack of clinical data in Ostlund et al. detracts from any allegations of a reasonable expectation of success in using chromium to treat PCOS as is presently claimed, particularly in view of the notoriously well-known unpredictability of pharmaceutical sciences as confirmed by the attached Declaration. A review of the Ostlund reference reveals that the patent is directed specifically to the use of pinitol in treating insulin resistance. At Column 3, lines 11-12, for example, the '166 patent describe that "[t]he present invention shows for the first time that insulin resistance in humans is directly treatable by pinitol." As described above, the de la Harpe patent does not mention insulin resistance and only discusses the treatment of conditions which may or may not be due to a patient having insulin resistance, as all of the conditions disclosed in the reference can have multiple causes. Because the composition and methods of de La Harpe lack pinitol, any derivative of pinitol, any metabolite of pinitol and any organic compound with a similar structure or function, there is no reason to believe that the composition of de La Harpe could be used successfully in the method claimed by Ostlund. Accordingly, a person of skill in the art would have no reasonable expectation that the substitution of chromium for pinitol would be effective in ameliorating the symptoms of PCOS. Absent a reasonable expectation of success in combining and/or modifying the '166 and '905 patents, these references cannot serve as a basis for an obviousness rejection.

At best, the use of chromium for treating PCOS might be considered obvious to try in view of the cited references. However, Applicants remind the PTO that "obvious to try" is not the standard for evaluating obviousness under 35 U.S.C. §103. See M.P.E.P. § 2145. The de la Harpe et al. reference merely discloses the use of chromium in lowering serum glucose levels, lowering serum lipid levels, and increasing lean body mass. The Ostlund et al. reference describes the use of a carbohydrate, pinitol, for treating insulin resistance. Again, given the fact that pharmaceutical sciences are unpredictable and the biological systems affected by a disease such as PCOS are complex, these references have little predictive value in ascertaining whether chromium would have therapeutic value in PCOS.

In contrast, the data resulting from the pilot study detailed in Exhibit B and discussed in the attached Declaration at, for example, ¶ 9 and ¶10, are unexpected in light of the prior art. The data provided by the National Institute of Health (NIH)-funded pilot study confirms the

present patent disclosure: it shows that chromium supplementation significantly reduces symptoms of PCOS and therefore offers promise to those individuals suffering from PCOS. See Exhibit B. The role of chromium in PCOS apparently was not obvious to the NIH, which funded the study to develop such data. The resulting data described in the Declaration and attached press release were unpredictable given the teachings of the prior art and the understanding in the field prior to the present invention. While one can, in hindsight, partially explain the results in terms of chromium facilitating insulin function, the efficacy of the use of chromium in treating PCOS was unpredictable prior to conducting the appropriate tests.

The prior art references fail to teach each and every limitation of the claims

Finally, in order to establish a case for obviousness, the Examiner must cite prior art that teaches or suggests all the claim limitations. See M.P.E.P. § 2143.03. It is well-established law that the PTO must give weight to all claim limitations. The present claims require the selection of a particular patient population, namely an individual suffering from PCOS that is neither targeted nor mentioned in the '905 patent. The '905 patent discloses a composition for supplementing dietary chromium and facilitating absorption of essential metals comprising chromic polynicotinate in combination with at least one of a cyclooxygenase inhibitor, an acid, a mucolytic, and a salicin containing herb. de la Harpe does not discuss insulin resistance nor does it contemplate the use of chromium in ameliorating the symptoms of PCOS as is presently claimed. The '166 patent describes the use of a carbohydrate, namely pinitol, in treating insulin resistance. Neither reference recites an identification step as is presently claimed in each independent claim, wherein an individual suffering from PCOS is identified. Moreover, neither the '166 nor the '905 patent disclose or suggest the administration of an essential metal, namely a chromium complex other than chromium yeasts, which are now specifically excluded from the claims by the present amendments, to reduce the symptoms of PCOS. Because the references do not disclose each limitation of the claims, the references fail to establish a *prima facie* case of obviousness.

The claimed invention possesses unexpected results over the prior art

In the previously submitted Amendment and Responses to Office Actions, Applicants asserted that there was no motivation to combine the cited references, and there would not have been a reasonable expectation of success in doing so. The Examiner has indicated that these

arguments were not persuasive. While Applicants respectfully disagree with the Examiner on these points, even assuming that there was motivation to combine the cited references and there was a reasonable expectation of success in doing so, the Examiner is still required to look at the objective indicia of non-obviousness.

The Federal Circuit has held that objective indicia of non-obviousness should be considered in every case for the probative value they have. *Stratoflex, Inc. v. Aeroquip Corp.*, 218 U.S.P.Q. 871, 879 (Fed. Cir. 1983); *See also, Gambro Lundia AB v. Baxter Healthcare Corp.*, 110 F.3d 1573 (Fed. Cir. 1997) (holding that objective indicia of nonobviousness are invariably relevant to a determination of nonobviousness). These objective indicia may often be the most probative and cogent evidence of nonobviousness in the record. *Id.* at 1579 (Fed. Cir. 1997). Secondary considerations include the unexpected properties of the claimed invention. *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998).

Applicants submit herewith the declaration of James Komorowski, M.S., Vice President, Technical Services and Scientific Affairs at Nutrition 21, Inc. and an expert in the field of nutritional supplementation with chromium. Additionally, please find a copy of a press release (Exhibit B), describing a NIH-funded pilot study wherein chromium picolinate supplementation was shown to be surprisingly effective and advantageous in the treatment of PCOS. This declaration and additional evidence submitted herewith establish the unexpected advantages of the claimed invention over the cited art.

Unexpected Advantages

The presence of a property not possessed by the prior art is evidence of nonobviousness. M.P.E.P. §716.02(a) (citing *In re Papesch*, 315 F.2d 381, 388 (C.C.P.A 1963)). "A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness..." M.P.E.P. §716.02(a); (citing *In re Corkill,* 771 F.2d 1496, 1501 (Fed. Cir. 1985). Furthermore, evidence that a compound is unexpectedly superior in one of a spectrum of common properties can be enough to rebut a *prima facie* case of obviousness. M.P.E.P. §716.02(a) (citing *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987)).

One important aspect of the claimed methods is the unexpected discovery that chromium supplementation serves to ameliorate symptoms associated with PCOS. See, e.g., page 10 of the specification; Declaration ¶ 9. Applicants' surprising findings, which were discussed and claimed in U.S. Patent Application Ser. No. 10/001,648, were confirmed by an independent

research group. See Declaration, ¶ 9. The results of the independent study revealed that insulin sensitivity in PCOS patients was significantly increased by an average of 35% after two months of treatment with chromium picolinate. See Declaration, ¶ 7 and Exhibit B. Moreover, baseline insulin levels decreased by 22% in women presenting with PCOS following chromium supplementation. *Id.* Applicants note further that, contrary to the position taken by the Examiner, the National Institute of Health appeared to think that chromium supplementation for the treatment of PCOS was sufficiently novel and promising to fund the pilot study conducted by State University of New York, Stony Brook. See Declaration, ¶ 7 and Exhibit B. Dr. Michael L. Lydic, assistant professor at SUNY Reproductive Endocrinology Division, who led the independent study detailed in Exhibit B, opined "[c]hromium picolinate, which has positive effects on insulin sensitivity in people with type 2 diabetes, looks like it has great potential as a safe, effective long-term therapy to fill a void in treating PCOS." See page 1-2 of Exhibit B. Dr. Lydic lends additional credence to Applicants' assertions that, prior to this invention, there was a dearth of effective and tenable treatment options for individuals suffering from PCOS. Dr. Lydic further notes "[i]f larger, controlled trials confirm chromium picolinate's efficacy, PCOS patients could potentially take the supplement every day to decrease their risk of diabetes and possibly improve other physical and symptomatic effects of PCOS."

In view of the deficiencies discussed above, the '166 and '905 patents are not sufficient to support a *prima facie* case of obviousness. Moreover, the objective indicia of non-obviousness set forth in the attached Declaration and Exhibit B militate against a finding of obviousness. Therefore, Applicants request withdrawal of this rejection.

Response to the Examiner's Interview Summary

Applicants wish to again thank Examiner Patten and her supervisor for participating in the telephonic interview on November 4, 2003. On November 7, 2003, Applicants filed a Request for Continued Examination and included an interview summary with the filing. Prior to receipt of the subject Office Action, Applicants had not received the Examiner's Interview Summary. According to the Examiner, a response to the Examiner's Interview Summary is now necessary.

The Examiner stated that the term "consisting essentially of" was discussed during the telephonic interview. Applicants' representatives argued that the phrase excluded material other than basic, inert carriers. According to the Applicants, inert carriers do not impact the basic and

novel characteristics of the invention. The Examiner reiterated her position that the phrase "consisting essentially of" included materials, which were found in the prior art for the same purpose/intended use, namely for the treatment of PCOS. As detailed *supra*, Applicants assert that the Examiner's definition of the basic and novel characteristic of the invention as merely the treatment of PCOS is erroneous. The invention is not simply the treatment of PCOS but rather, Applicants have discovered that chromium specifically ameliorates many of the symptoms associated with PCOS. This was not previously known. As claimed in Claim 16, for example, Applicants have shown that chromium in the absence of other pharmaceutically active compounds acts to reduce the symptoms associated with PCOS. The basic and novel characteristic of Claim 16 and those claims depending therefrom is the appreciation that chromium complexes can be used alone (i.e. in the absence of other pharmacologically active ingredients) to reduce PCOS. This appreciation stands in stark contrast to the prior art. The art cited by the Examiner as a basis for rejecting the claims as obvious teach multi-component formulations comprising numerous bioactive ingredients to treat etiologically distinct ailments. For example, the de la Harpe et al. reference discloses the use of chromium in combination with five other ingredients for, *inter alia*, lowering blood glucose and serum lipid levels. The Ostlund et al. reference discloses the use of pinitol for treating insulin resistance. Applicants disagree with the Examiner and note that ingredients other than chromium and basic, inert carriers do materially change the invention.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that the present application is in condition for allowance. Nevertheless, the PTO is invited to contact the undersigned at the telephone number appearing below to discuss any remaining issues. Any claim amendments which are not specifically discussed in the above remarks are made in order to improve the clarity of claim language, to correct grammatical mistakes or ambiguities, and to otherwise improve the capacity of the claims to particularly and distinctly point out the invention to those of skill in the art.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: March 1, 2004

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